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Review

The effect of natural antimicrobials against *Campylobacter* spp. and its similarities to *Salmonella* spp, *Listeria* spp., *Escherichia* coli, *Vibrio* spp., *Clostridium* spp. and *Staphylococcus* spp

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ABSTRACT

The increased resistance of campylobacters to antibiotics required the identification and isolation of novel antimicrobials able to inhibit its virulence, to cause less or no resistance and display no host toxicity. Acquiring all this knowledge was only possible through a better understanding of their antibacterial potency and of the biological mechanisms involved attenuating the bacterial virulence factors. This review describes the most recent developments in the area by looking at the new antimicrobial interventions aiming to combat the transmission and colonisation of *Campylobacter* spp. and its commonalities with other pathogenic bacteria. In this review we are also looking into the most recent developments, both *in vitro* and *in vivo*, focusing on the biological mechanisms by which natural antimicrobials express their anti-pathogenic effect. Following this extensive literature search we conclude that further studies are essential to elucidate the efficiency of plant, animal, bacteria and marine-derived antimicrobials as well as their role as promising alternatives to antibiotics.

1. Introduction

There is an increased interest in the identification of dietary interventions aiming to reduce the presence of antibiotic-resistant bacteria (Drame et al., 2020; Yang et al., 2019). To achieve this, the strategy includes supplementation of animal feed with biologically active substances (e.g. essential oils, phenolics, organic acids, peptides, etc.) with pronounced antimicrobial activity against a wide spectrum of pathogens (Aziz & Karboune, 2018; Sima et al., 2018). The approach involving natural antimicrobial formulations enriched with organic acids and plant extracts is a promising candidate for a successful pathogen control (Singh et al., 2015). They can be utilized as novel feed additives in the animal diet to fortify the animal immune system, to promote intestinal health and weight gain (Sima et al., 2019). Commercially available natural antimicrobials were able to significantly reduce the virulence of pathogenic microorganisms in poultry and shrimps in *in vitro* assays (Pinkerton et al., 2019; Sima et al., 2018). The successful identification of novel natural antimicrobials involves interdisciplinary approaches and technological updates in order to promote them as novel level drug. Furthermore, the application of biotechnology, molecular biology, pharmacognosy, ethnopharmacology and genetics in a whole integrated ensemble may play a valuable role as a key-tool in the development of novel antimicrobials.

Host safety must be a priority during the initial stages of development for these natural alternatives placing cytotoxicity investigations at the core of the research to ensure that little or no secondary effects are expressed as often seen in the case of antibiotics. Because of their low toxicity, plant extracts have been studied extensively especially in

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traditional medicine for treatment of diabetes, inflammation, and microbial disorders (e.g. *Murraya paniculata*) (Menezes et al., 2015). The low toxicity levels expressed by plant antimicrobials extends to simpler compounds, like antimicrobial peptides (AMPs). For example AMPs obtained from *Citrus* spp. (citrus-amp1 and citrus-amp2) have been proven to be safer or at least similar in cytotoxicity when compared to AMPs from amphibians (Hylin-a1, K^0–W^6-Hy-a1 and Ocellatin 4-analogue) or from porcine (Tritrpticin) classifying them as an essential alternative in controlling bacterial pathogens (Inui Kishi et al., 2018). The same need for low toxicity of plant extracts applies also in clinical situations. The investigations of *Lawsonia inermis* extracts against clinical isolates of *Escherichia coli*, *Salmonella typhi*, *Klebsiella spp.*, *Shigella sonnei* and *Bacillus subtilis, Staphylococcus aureus*, *Staphylococcus epidermidis* was associated with a significant antibacterial effect and more importantly no signs of toxicity were observed when tested in mice (Gull et al., 2013).

For *Campylobacter* spp., as well as for the other related pathogens, acquiring antibiotic resistance represents a real issue for the poultry industry and the consumer. Natural antimicrobials interconnected with their multipotential ability to inhibit the multidrug-resistant pathogens provide a competitive alternative to antibiotics (Naeim et al., 2020; Wright, 2019). The biological mechanisms by which natural antimicrobials prevent the growth and development of pathogens is still not well understood, however significant advances have been made in the case of *Campylobacter* spp. (Sima et al., 2018) describing their anti-virulent effect rather the microbial killing effect. Most of these mechanisms are generally assigned to natural antimicrobials derived from plants (polyphenols, essential oils), animal metabolites, marine inhabitants (algae extracts), or microorganisms (organic acids, fermentation by-products) and are mechanisms of interests to combat pathogens. The chemical composition of plant constituents is strongly correlated with their antimicrobial capacity. For example, hydroxyl (-OH) present groups can interact with bacterial cell membranes and cause a breakdown of its structures, generating cell membrane lysis and bacterial death (Quinto et al., 2019). Gram-negative bacteria are frequently less susceptible to antimicrobials compared to Gram-positive bacteria due to the presence of an outer membrane layer (Djihane et al., 2017) that comprise hydrophilic lipopolysaccharides providing a particular barrier to different antimicrobial molecules and hydrophobic compounds as substances presented in essential oils (Hyldgaard et al., 2012). Additional targets of essential oils and their modes of actions have been discussed previously (Hyldgaard et al., 2012). Most of antimicrobial compounds are of organic origin, e.g. reuterin which is biosynthetically produced from glycerol by *Lactobacillus reuteri* and known for its role in neutralizing the lipopolysaccharides in *Porphyromonas gingivalis* (Han et al., 2020). Reuterin was earlier described as an effective antimicrobial in suppressing the logarithmic growth of *C. jejuni* with ≈4 log CFU/mL (Asare et al., 2020). The main antibacterial properties of reuterin were attributed to the acrolein fraction (Asare et al., 2018), also called the active antimicrobial fraction (Engels et al., 2016).

Many reviews have been published in the last 10 years discussing the effect of natural antimicrobials against bacterial pathogens (Fan et al., 2018; Juneja et al., 2012; Tiwari et al., 2009). We will aim in this review to discuss the most recent developments in using natural antimicrobials to reduce *Campylobacter* spp. colonisation of poultry and discuss the biological mechanisms behind the observed effects of natural antimicrobials. Moreover we will approach and discuss the effects on *Campylobacter* spp. and other related pathogenic bacteria in relation to their response to natural antimicrobial usage.

2. The current view on *Campylobacter* spp

Campylobacter spp., are a spiral shaped, Gram-negative and oxidase positive microaerophilic bacteria with a single polar flagellum (Igwaran & Okoh, 2019). The genus *Campylobacter* includes 37 taxa of which 31 are species and 11 are subspecies (Miller & Yee, 2019). Bacteria of this genus are responsible for causing gastrointestinal disorders in humans, the so-called campylobacteriosis, in particular following consumption of contaminated poultry meat but can also be present in water, milk and other food products (Karki et al., 2019; Man, 2011; Sheppard et al., 2010). Many reviews have been published recently discussing the role of individual natural antimicrobials in preventing colonisation or reducing *Campylobacter* spp. virulence with one of the latest one (Klančnik et al., 2020) also discussing their role in preventing biofilm formation but without linking the effects to other related pathogens present within the same biological niche. In Table 1 we describe the effect of recently characterized antimicrobials against *Campylobacter* spp.

Because of its impact on human health, increased antibiotic resistance in *Campylobacter* represents a huge issue for public health. Even though the use antibiotics as growth stimulators is banned in the EU since 2006, many countries around the world still use such practices, and this has contributed to the continuing rise in bacterial antibiotic resistance. The consequences of overuse of antibiotics followed by acquired bacterial resistance recommends the development of novel antimicrobial strategies including the use of plant extracts or the so called plant phenolics. These phenolic metabolites can change the pH, modify efflux pumps, influence membrane permeability of microbes and reduce bacterial virulence, for example, via the inactivation of the type VI secretion system (T6SS) as previously reported (Srivastava et al., 2014; Stratakos et al., 2019). The efflux system is of particular interest because it has been shown that the use of sub-inhibitory concentrations of natural antimicrobials can modulate their activity (CmeABC), resulting in an increased anti-campylobacter effect (Možina et al., 2018).

Another mechanism by which natural antimicrobials are expressing their anti-bacterial effect against *Campylobacter* spp. is exemplified in the literature by the activity of selected organic acids such as propionic, lactic, formic, acetic, butyric and citric acids. For example, they have been identified as potent inhibitory agents against *C. coli* swine isolates (Beier et al., 2018). Moreover, antimicrobial mixtures, including combinations of organic acids and plant extracts, had a more efficient antimicrobial activity against *C. jejuni*, *C. coli* and other pathogens by acting directly or indirectly against their main virulence factors (Pinkerton et al., 2019; Sima et al., 2018, 2019; Stratakos et al., 2017, 2019a, 2020). More specifically, combinations of citric and lactic acid inhibited the virulence of *Campylobacter jejuni*, *in vitro*, via downregulation of the *hcp* gene expression which is part of the bacterial Type 6 Secretion System (T6SS) known for its involvement in virulence. Additionally, virulence factors such as motility and biofilm production were also inhibited (Sima et al., 2018). The *in vitro* results were also replicated *in vivo*, where the mixture was responsible for 3–4 log CFU/mL reduction in the cecum colonisation (Sima et al., 2018). Same study indicated that these mixtures of organic acids were able to modulate the transcription of *cet*B and *hcp* genes in *C. coli* and *C. jejuni* T6SS positive strains, genes proven to be involved in host colonisation (Sima et al., 2018). Another natural antimicrobial with similar effects was carvacrol, which is the active ingredient in oregano oil (Sharifi-Rad et al., 2018), and it seems that this extract has a direct and an indirect effect against *Campylobacter* spp. Its direct effect was described *in vitro*, where carvacrol was able to reduce *Campylobacter* spp. adhesion and invasion of epithelial cells and also inhibit biofilm formation (Kelly et al., 2017). The mechanism behind the reduced virulence effect involves disruption of bacterial outer and inner membrane integrity and reduction in biofilm formation via quorum sensing (Bassler, 2002). The indirect effect, *in vivo*, involves changes in the cecal microbiota leading to reduction in colonisation via competitive exclusion due to the increased presence of *Lactobacillus* spp. (Kelly et al., 2017).

The efficiency of their anti-campylobacter effect is also dependent on the bioavailability and the source of the antimicrobial compounds also affect their efficiency. A good example on how bioavailability affects efficiency is the use of eugenol. Its incorporation as nanoemulsions,

Table 1
The latest updates on natural antimicrobials compounds used against. *Campylobacter* spp.

Compound	Species	Concentration	Effects	Gene/Protein	Reference
Blackberry/Blueberry phenolic extract and *L. casei*	*C. jejuni* (ATCC BAA-1062)	0.1 mg/mL−1	Inhibitory, anti-invasive/ adhesive	↓CiaB, CdtB; ↑*flaA, flaB*	(Tabashsum et al., 2019)
Thymol Carvacrol	*C. jejuni* (NCTC 11168)	0.25 x MIC	Anti-adhesive	n.i.	Klančnik et al. (2020)
Pinot noir skin or seed extract and resveratrol	*C. jejuni* (K49/4)	200 μg/mL	Morphological changes		
Juniper fruit extract		1 mg/mL	Anti-adhesive, inhibitory		Klančnik et al. (2018a)
Alpinia katsumadai seed extract Epigallocatechin gallate	*C. jejuni* (11168)	50 μg/mL-1	Anti-adhesive		Klančnik et al. (2018b)
Pinocembrin	*C. jejuni* (11168), *C. jejuni* (11168ΔcmeR)	16-32-128 μg/ mL	Anti-adhesive, iron metabolism, anti-virulent	↑*Cj1153, FliK, FlaC, FlgE2, FlaA, FlgB, FlgD, Cj414, Cj415, Cj1338, PglJ, HtrA;* ↓*Cj0864, Cj1358c, RpsD, RpsK, RpsM, RpsA, RpmG, AspA, RpsD, CstA, NrfH*	Klančnik et al. (2019)
Probiotic *Lactobacilli*	*C. jejuni*	10^7–10^8 CFU	Inhibitory, bactericidal, anti-invasive, motility, immunomodulating	↓*flaA, flaB, flhA, ciaB, luxS*	(Taha-Abdelaziz et al., 2019).

Compound	Species	Concentration	Effects	Gene/Protein	Reference
Sophorolipid, lactic acid	*C. jejuni* (ATCC 33560™)	½ MIC	Inhibitory, synergystic	n.i.	Silveira et al. (2019)
Probiotic *Lactobacillus* isolates	*C. jejuni*, *C. coli*	MIC	Inhibitory		(Dec et al., 2018)
Phyllospongia papyracea	*C. jejuni* (ATCC 33291)	2 μg/mL			Sun et al. (2017)
Eugenol	*C. jejuni* (S1, S3, S4, S8)	7.61–121.8 mM			Wagle, Arsi, et al. (2019)
Eugenol		0.0125%	Motility, anti-QS, inhibitory, stress response	↓ MotA, MotB, KatA, *luxS*	Wagle, Arsi, et al. (2019)
Chitosan			Inhibitory, motility	↓MotA; ↑CiaB, JlpA, SodB	
Chitosan with eugenol		2%	Motility, anti-QS, inhibitory, stress response	↓*motA, luxS, katA, cetA.* ↑*motB, ciaB, jlpA, sodB*	
Pectin with eugenol			Inhibitory	failed	
Arabic gum/chitosan with carvacrol		10%, 2%; 0.25–1%	Motility, energy taxis, anti-adherence, inhibitory	↓CetB, MotA, CadF, JlpA	Shrestha et al. (2019)
Carvacrol		0.0125%	Motility, energy taxis, anti-adherence, inhibitory	↑*cetB*	

Compound	Species	Concentration	Effects	Gene/Protein	Reference
Oregano EO Oregano EO + PEF Lemongrass, garlic, thyme EO	*C. jejuni* 1145 DF, *C. jejuni* 1354 DF, *C. jejuni* 11168, *C. jejuni* (ATCC 33560)	62.5–4000 ppm	Inhibitory	n.i.	(Clemente et al., 2020)
Trans-cinnamaldehyde Carvacrol Eugenol	*C. jejuni* 11168	75.64 mM 66.56 mM 60.9 mM	Anti-biofilm, motility, stress response	↓*flaA, flaB, flgA;* ↑*luxS* ↓*flaA, flaB, flaG, flgA, waaF, cosR, ahpC*	Wagle, Arsi, et al. (2019)
Sedum roseum extract	*C. jejuni* 11168, *C. jejuni 11168ΔluxS*	0.25 x MIC	Anti-QS, motility, anti-adhesive	n.i.	Šimunović et al. (2020)
Juniper, clove, lavender EO			Motility		
Oregano flower extract			Motility, anti-adhesive		
Rosmarinic acid and γ-terpinene			Motility		
Rosemary EO *Satureja montana* EO			Anti-adhesive		
Nettle extract			Motility		
Carvacrol			Anti-adhesive/invasive		

Compound	Species	Concentration	Effects	Gene/ Protein	Reference
TYPLEX® Chelate and TYFER™ (ferric tyrosine)	*C. jejuni*	0.02–0.20 g/kg; 20 mg/kg feed	Anti-biofilm, inhibitory, growth promoter, protective		(Khattak et al., 2018), (Skoufos et al., 2019), (Bampidis et al., 2019)
Reuterin	*C. jejuni, C. coli*	1.5–5.8 μM	Bactericidal, inhibitory		Asare et al. (2020)
Organic acids	*C. coli*	11–35 mM	Inhibitory		Beier et al. (2018)
Auranta 3001	*C. jejuni* RC039, *C. coli* RC013	0.1–0.5%	Anti-invasive/adhesive, motility, inhibitory	↓*hcp*, *cet*B	Sima et al. (2018)

emulsions and suspensions was reducing, *in vitro*, the presence of *C. jejuni* on chicken skin when applied as washing treatments on the carcass (Basanta et al., 2019). The authors concluded that incorporation of eugenol at 2% in chitosan, as a coating preservative agent on chicken wingettes, resulted in a 3 log CFU/sample reduction after seven days of storage (Wagle et al., 2019). Similarly, pectin fortified with 2% of eugenol showed a reduction of ≈2 Log CFU/sample. Additionally, exposure of *C. jejuni* to the chitosan-eugenol combination induced changes in bacterial genes involved in motility, quorum sensing and oxidative stress clearly indicating its anti-virulent activity. Similar products prepared from arabic gum (10%) and chitosan (2%) fortified with carvacrol (0.25–1%) also reduce the load of *C. jejuni* on chicken wingettes (Shrestha et al., 2019). The authors concluded that wingettes treated with sub-lethal concentrations of carvacrol, chitosan itself or mixed together demonstrated a significant effect on the expression of genes responsible for motility (*motA*), energy taxis (*cetB*), fibronectin-binding (*cadF*) and adherence (*jlpA*) as well the coatings presented to effectively reduce logarithmically growth loads of *C. jejuni* from day 0 till day 7. Concerning the source, anti-campylobacter molecules have been identified in large variety of organic compounds. The recently identified antimicrobial compound, 2-(3′,5′-dibromo-2′-methoxyphenoxy)-3,5-dibromophenol isolated from a marine sponge (*Phyllospongia papyracea*) had displayed an inhibitory (MIC 2) activity against *C. jejuni* ATCC 33291 (Sun et al., 2017). Similarly, an earlier study described the anti-campylobacter activity of resveratrol-hydroxypropyl-γ-cyclodextrin inclusion complexes. These complexes with resveratrol showed an anti-quorum sensing activity being able to prevent the biofilm formation at sub-inhibitory concentrations against *C. jejuni* 225421 and *C. coli* 873 (Duarte et al., 2015).

Inhibiting or affecting the phenotypic traits of *Campylobacter* will potentially have major implications on its pathogenic behavior and recently over 20 natural extracts were described as potential phenotypical modifiers (Šimunović et al., 2020). Of these, the ethanolic extract of roseroot (*Sedum roseum*) significantly affected the quorum sensing signaling (96%), reduced the swarming motility (35%) and adhesion to polystyrene by ≈ 1.41 log CFU/well. Such findings could be attributed to the presence of the biologically active compounds such as phenylethanoids, procyanidin-catechin derivates, cyanogenic glycosides, flavonols, phenylpropanoids and monoterpenes (Alperth et al., 2019). Additional decreasing effects on motility were detected in essential oils from juniper, cloves (*Syzygium aromaticum*), lavender (*Lavandula hybrida*), ethanolic fractions of oregano flowers (*Origanum* spp.), nettle (*Urtica dioica*) as well as singular purified compounds such as rosmarinic acid and γ-terpinene (Šimunović et al., 2020). Suggestively, the author stated that mentioned above natural antimicrobial complexes are involved in motility processes via modulation of *C. jejuni* LuxS/QS. Moreover, the *C. jejuni* 11168 attachment on the polystyrene surface was greatly decreased (26%–99%) after application of 0.25 × MIC concentrations. Interestingly, the adhesion rate of *C. jejuni* 11168 Δ*luxS* was reduced in comparison to wild type *C. jejuni* 11168, indicating the involvement of *luxS* mediated intercellular signaling pathways in adhesion to abiotic surfaces (Šimunović et al., 2020). The adhesion is also inhibited when we refer to adhesion to eukaryotic cells. Co-incubation of *C. jejuni* with oregano flower, winter savory (*Satureja montana*) extracts and γ-terpinene at MICs (0.25) within 16h conferred a significant anti-adhesive capacity on the human epithelial cell line INT407. Despite anti-adhesive properties, 15 of natural extracts demonstrated to reduce the invasiveness of *Campylobacter* toward INT407 cells, of which carvacrol showed the most efficient potential (Šimunović et al., 2020).

There is also sufficient new evidence in regards to the efficiency of plant extracts in reducing *Campylobacter* contamination of industrial surfaces. For example similar findings were reported concerning the anti-campylobacter activity of phytochemicals with a safe status, describing the antimicrobial mechanistic insights highlighting the efficacy of trans-cinnamaldehyde, eugenol, and carvacrol as anti-biofilm disinfectant agents. These phytocompounds significantly decreased the biofilm formation on stainless steel, and polystyrene surfaces at both 20 °C and 37 °C. The highest concentrations of trans-cinnamaldehyde (75.64 mM), eugenol (60.9 mM) and carvacrol (66.56 mM) resulted in the inactivation of *C. jejuni* biofilm development on the steel surfaces reducing bacterial loads by ≈ >7 log CFU/mL at 20 °C after only 5 min of treatment (Basanta et al., 2019). All three plant-derived compounds induced a significant downregulation of genes involved in motility, the major phenotypic characteristics involved *Campylobacter* adhesion abilities. Moreover, using scanning electron microscopy it has been revealed that these plant extracts (e.g. eugenol) induced disruptive effects the biofilm formation. In particular, eugenol was able to modulate the expression of the genes involved in bacterial stress response such as *ahpC & cosR*, and in the cell-surface associated gene *waaF* (Basanta et al., 2019).

How these extracts or natural antimicrobials act *in vivo* and how available they are to the end user depends on the ability of the producer to supply high quality scientific data in regards to their effect. One such example is the commercially new product TYPLEX® Chelate containing ferric tyrosine as an organic molecule and which successfully inhibited *C. jejuni* biofilm formation in an *in vitro* plastic bead model (Khattak et al., 2018). Furthermore, *in vivo* administration of non-antibiotic TYPLEX® Chelate as a novel feed supplement in the chicken diets resulted in decreasing *C. jejuni* cecal loads by ≈ 2 log CFU/g and increasing cecal volatile fatty acids concentrations. These findings were identified also in other studies showing similar reductions in ($p = 0.004$) *C. jejuni* detection following supplementation with ferric tyrosine leading to a significant inhibitory potential against *C. jejuni* colonisation without negatively affecting growth performance parameters (Skoufos et al., 2019). An additional positive effect observed was the protective role against coccidiosis caused by a natural infection by *Eimeria tenella* (Skoufos et al., 2019). According to the European Food Safety Authority (EFSA) it was concluded that a similar antimicrobial product TYFER™ (ferric tyrosine) could be included in animal feeds in order to effectively decrease *Campylobacter* spp. loads in the cecal content without posing health risks adversely to the birds and environment (Bampidis et al., 2019).

Overall, this data suggests there is an increase in our understanding of the biological mechanisms involved in the observed effects of natural antimicrobials. At least in the case of *Campylobacter*, more suitable *in vivo* animal models as well as further genetic investigations are needed for a more precise characterization of possibly caused genomic mutations following exposure to natural antimicrobials.

3. Similarities to *Salmonella* spp

Campylobacter infections are often associated with *Salmonella* infections in humans first due to their clinical similarities and secondly due to the similarities in clinical treatment by using antibiotics as proton pump inhibitors (PPI) to reduce symptoms severity (Esan et al., 2017). The area is not very well studied in *Salmonella* but despite the lack of literature there is evidence in other bacteria that plant extracts can be efficient efflux pump inhibitors (EPIs) and represent a potentially patient-friendly strategy for controlling *S. aureus*. (Espinoza et al., 2019). However, using natural antimicrobials to prevent *Salmonella* colonisation/infection will be of major importance since it has been demonstrated that not only *C. jejuni* colonisation was increased but also the clinical signs of campylobacteriosis when mice were co-infected with *C. jejuni* and *Salmonella typhimurium* (Wang et al., 2018).

Despite major outbreaks and financial costs caused by the genus of *Salmonella*, alternative methods have been proposed to limit the transmission of this pathogen in different industrial settings. Furthermore, due to the European Union ban on using antibiotics as growth promoters in livestock or other agriculture domains, a new trend has emerged. The so-called antimicrobial growth promoters (AGP) or non-AGPs which are non-antibiotic feed supplements focusing on the increase of animal

growth, as well to improve their health status which could be used as a suitable tool to control salmonellosis as well other foodborne pathogens in animal sectors (Aljumaah et al., 2020).

To avoid the detrimental impacts on animals, natural antimicrobial products such as phytobiotics, organic acids and probiotics can be alternatively applied within animal diet. From the commercially available probiotics designed for on-farm pathogen control CloStat®, Bacillus Blend®, GalliPro® demonstrated significant inhibitory potential after *in vitro* evaluation of *Salmonella Typhimurium* and other pathogens (Aljumaah et al., 2020). Similarly, phytobiotics namely Nor-SpiceAB®, Sangrovit®, MixOil® and organic acid Fysal® presented prominent MIC and MBC indices. Furthermore a recent *in vivo* study aimed to investigate the antimicrobial efficacy and protective activity of different natural feed additives in *Salmonella* challenged chicken broilers infected with *Salmonella enterica* subsp. *Typhimurium* (Abudabos et al., 2019). The results showed a significant decrease in broiler production indices and histological parameters in the *Salmonella* infected groups. However, supplementation with natural feed additives was able to lessen the adverse effects of salmonellosis. Of these, the administration of Sangrovit®, Varium™ and CloStat® demonstrated the highest efficiency. The authors concluded that the administration of such natural antimicrobials in the bird's diet was able to reduce the harmful outcomes of salmonellosis by enhancing the gut health conditions and increasing growth performance simultaneously.

In *Salmonella* intense attention has focused on polyphenolic compounds isolated from marine dwellers, including brown seaweed. Two representatives *Ascophyllum nodosum* and *Fucus serratus* were reported to contain a high content of phenolic compounds such as phlorotannins (Ford et al., 2020). This study concluded that phlorotannin extracts have an antimicrobial action against *Salmonella agona* through the modulation of bacterial outer membrane permeability and intracellular ATP levels. *A. nodosum* showed a more pronounced MIC presenting values of 1.56 mg/mL and MBC indices of 3.125 mg/mL, respectively. While *F. serratus* presented slightly increased MICs including concentrations of 3.125 mg/mL and MBC displayed 6.25 mg/mL. Besides, both extracts exhibited low cytotoxicity values on intestinal porcine epithelial cell line (IPECJ2) after MTT assay investigation. Hence, their study indicated that *F. serratus* and *A. nodosum* extracts could be applied alternatively to antibiotics or zinc oxide in pig diets to combat bacterial infections. Likewise, the addition of caproic acid and allyl isothiocyanatein the diet showed to decrease the counts of *S. enteritidis* below the limit of detection in a chicken simulated digestion model (Oliveira et al., 2019).

4. Parallels with *Listeria* spp

In contrast to *S. typhimurium*, co-infection by *Listeria monocytogenes* seems to have little positive effect on *C. jejuni* colonisation or infection (Wang et al., 2018). *Listeria* spp. bacteria are rod-shaped, Gram-positive and are amongst other the most commonly encountered spoilage microorganism found in various food products and factory surfaces that can cause a life-threatening disease known as listeriosis (EFSA-ECDPC, 2018). The main pathogen *Listeria monocytogenes* triggers listeriosis which usually occurs in humans or animals and is described to provoke a high mortality and morbidity rate in new-borns, people with immunodeficiency, including older people (Stratakos et al., 2020).

Early research in natural antimicrobials has emphasized convincingly *in vitro* and *in vivo* effectiveness of different bio-active mixtures enriched with plant-derived compounds and organic acids acting through indirect or direct anti-virulence against a wide range of food and foodborne pathogens (Pinkerton et al., 2019; Silveira et al., 2019; Sima et al., 2018, 2019; Stratakos et al., 2017, 2018, 2019a, 2019b). For example the antimicrobial mixture Auranta 3009 (citrus extract - 6%, grape seed extract - 2%, and oregano extract - 1%), applied at 0.2% concentration, showed potent anti-listeria activity, *in vivo*, when used against artificially challenged mice (Stratakos et al., 2020). Specifically, the application of the mixture induced a remarkable decrease in the adherence rate of *L. monocytogenes* (OT171-4) isolates toward human intestinal cells (HCT-8). These *L. monocytogenes* (OT171-4) isolates from Hungarian vegetable batches involved in listeria outbreak, were considered to behave in a more strikingly invasive way compared to the reference strains (EFSA-ECDPC, 2018; Stratakos et al., 2020). The most distinctive potential of the mixture was conferred due to an *in vivo* model investigation results. The *ad libitum* administration of the mixture (0.5%) in drinking water, indicated significant mitigating effects against the induced listeria infection as it was noticed at liver and spleen level of the animals (Stratakos et al., 2020).

Natural antimicrobial compounds from essential oils could interfere with the balance of *Listeria* catabolic processes through the induction of metabolic shifts by replacing oxidative processes to fermentation ones (Braschi et al., 2018). Polyphenolic extract from olive oil, noni fruit extract, tea tree (*Melaleuca alternifolia*) essential oil, propolis extracts, dehydro-δ-viniferin, bacterial metabolite ε-Poly-lysine, were reported for significantly destructive effects induced in the cell membrane of listeria isolates indicating suitable applicability for the food industry (Bouarab Chibane et al., 2019; Guo et al., 2019; Kang & Song, 2019; Lin et al., 2018; Mattio et al., 2019; Pobiega et al., 2019; Silva et al., 2019). For example, lemongrass (*Cymbopogon citratus*) essential oil, due to the presence of monoterpene fraction, showed a significant anti-listerial potency via impacting the structure of biofilms after microscopical observation (Reis-Teixeira et al., 2019). Analogously, polyphenols from kiwi peel (*Actinidia chinensis*) and crab apple tree bark (*Malus baccata* and *Malus toringoides*) presented very efficient antimicrobial activity towards *L. monocytogenes* and other food-related pathogens (Alim et al., 2019; Elansary et al., 2020). Food products such as cantaloupe and catfish fillet treated with the extracts of pecan shell nuts (*Carya illinoinensis*) was able to decrease *L. monocytogenes* counts in food matrices (catfish fillets and cantaloupes) in a noticeable way (Yemmireddy et al., 2020). Likewise, leaf ethanolic extract of *Eucalyptus camaldulensis* at sub-inhibitory concentration was responsible for impairing of listeriolysin O production, simultaneously inhibiting swarming motility up to 80% as well displayed a good anti-biofilm activity versus *L. monocytogenes* (F2365) isolate (Ozioma Forstinus Nwabor et al., 2019).

The development of bacteriocins and bacteriophage-based strategies are seen nowadays as a substitute antibiotics in food, agriculture and medicine (Ben Lagha et al., 2017; Guitián et al., 2019; Komora et al., 2020; Lei et al., 2020; Lewis et al., 2019; Moye et al., 2018; O'Connor et al., 2020). Interestingly, recent studies had indicated that when *L. innocua* was co-cultured with *L. lactis* (nisin producing) there were significant microscopic differences in spatial organization and colony size with effect on microbial adaptation and environmental stress response (Costello et al., 2020).The antibacterial efficacy of bacteriocins can be enhanced by fusion in a mixture with essential oils (Churklam et al., 2020). For example carvacrol in combination with nisin displayed promising inhibitory synergetic efficiency by retarding the growth of listeria in a real food matrix model (Churklam et al., 2020).. Another combination, aiming for an anti-listerial effect, consisted in the application of bacteriophage Listex™ (P100), bacteriocin pediocin (PA-1) mixed with HHP (mild to high hydrostatic pressure) to reduce the viability of *L. monocytogenes* in milk (Komora et al., 2020). Another study suggested a third combination, consisting of P100 and Nisaplin®, had a successful applicability at an MOI of 2.5 resulting in a significant ($p \leq 0.001$) logarithmic decrease in *L. monocytogenes* counts at ten days after inoculation in the coleslaw matrix at 4 °C (Lewis et al., 2019)..

5. Connections with *Escherichia coli*

Similarly to *Listeria monocytogens*, pathogenic *E coli* seem to also have little effect on *Campylobacter* spp colonisation levels (Wang et al., 2018). They seem however to be connected from a clinical point of view since it has been reported that co-infections of *C. jejuni* and *E. coli* O157 was associated with a waterborne outbreak (Bopp et al., 2003). This

particularly interesting since bacterial infections are generally attributed to a single microorganism (Forbes et al., 2009).

Similarly to *Campylobacter* diversified phenolic compounds were also described to exhibit remarkable antibacterial activity versus a broad spectrum of *Escherichia coli* isolates (Dávila-Aviña et al., 2020; Ford et al., 2020; Hendrich et al., 2020; Ng et al., 2019; Yalcin et al., 2020). Of these, newly reported phlorotannins isolated from brown seaweeds, specifically *A. nodosum* and *F. serratus* phenolic extracts presented marked bacteriostatic and bactericidal indices against *E. coli* O157 (Ford et al., 2020). Furthermore, they were able to decrease intracellular ATP levels significant and to impair cell membrane permeability depending on the phlorotannin concentration. Simultaneously, it was elucidated that the extracts do not induce cytotoxicity in the swine cell lines (IPECJ2). An earlier study reported similar antimicrobial mechanistic insights of carvacrol, denoting a pronounced efficacy versus clinically important Shiga toxin-producing *E. coli* (STEC) and non-STECs strains (Stratakos et al., 2018). Additionally, carvacrol was capable of decreasing adherence of STEC strains towards human intestinal epithelial cells using the *in vitro* gentamicin protection infection model. The application of carvacrol, in combination with mild heat, demonstrated to behave in a synergistic manner, which resulted in acting through a significant inactivation of heat-resistant *E. coli* (ATCC 43888) strain (Gayán et al., 2020).

The biological mechanism behind the natural antimicrobials mode of action has been described in recent findings concerning the anti-virulence strategies illustrating their ability to significantly attenuate virulence characteristics of Shiga-like toxin-producing *E. coli* O157: H7 (Stratakos et al., 2018, 2019a, 2019b). One mixture identified as having these abilities was based on the combination of the lactic, citric acid and the citrus extract (Stratakos, Linton, Ward, Campbell, et al., 2019). The application of this mixture using an *in vitro* rumen model revealed a noticeable gradual logarithmic decrease of *E. coli* O157 counts in comparison to the control. Simultaneously, the combination proved to alleviate the biofilm production capacity in a significant manner. The study confirmed that the antimicrobials were able to decrease particularly bacterial swarming motility and to reduce the production of exopolysaccharides. However, no interfering effects on *E. coli* quorum sensing ability were observed. Lately, another study suggested anti-virulence therapy of the mixture based on organic acids (lactic and citric acid) and plant extracts (oregano, grape, citrus) as a feed additive (Stratakos, Linton, Ward, Sima, et al., 2019). The study shows that sub-inhibitory concentrations (0.1 and 0.5%) appeared to significantly reduce bacterial motility and the adhesion rate of *E. coli* O157 to the HCT-8 epithelial cell line. The antimicrobial mixture was also responsible for suppressing the expression of Shiga like toxin 2 (*stx*2) and adhesion (*eae*) genes, respectively indicating the anti-pathogenic effect.

Similarly to *Campylobacter*, in *E. coli* bacteriocins were also reported for their role in mitigating the overexploitation of antibiotics, especially in the farming sector (Ben Lagha et al., 2017). So far, different *Lactobacillus* species were capable of producing bacteriocins as well as inhibiting the growth of *E. coli in vitro* studies resulting in an enhanced health status of birds in contrast to uninfected control subjects (Ben Lagha et al., 2017). Along similar lines, according to O'Connor et al., it was concluded that natural antimicrobials could play a significant role in the future food and feed industries as they elicit increased antibacterial activity and presents a notable bio-preservative potency (O'Connor et al., 2020). A typical example is bacteriocin zrx03 which had a significant inhibitory effect against *E. coli* JM109 (ATCC 67387) and other foodborne pathogens (Lei et al., 2020). It can be concluded that plant and bacterial produced molecules exhibit a notable antioxidant activity and great bacteriostatic effects against *E. coli* (Rajoka et al., 2019; Xiao et al., 2020) and that there is an un-verified possibility that natural antimicrobials can reduce the possibility of *Campylobacter* infections due to a prior *E. coli* infection.

6. Links to *Vibrio* spp

Another health and food safety concern is caused by the water-borne and food-meditated pathogens from the genus *Vibrio* with more than 100 species within each at least 12 being responsible for triggering of human and animal infections (Jung, 2018). *V. parahaemolyticus, V. cholerae, V. vulnificus* and *V. alginolyticus* were reported among the most virulent species. From an economic point of view the genus *Vibrio* significantly impacts the aquaculture industry, causing acute mortality incidences in aquatic crustacean and fish species. *Vibrio* spp. as well as *Campylobacter* spp. cause severe gastroenteritis animals and humans but unlike *Campylobacter* the main source of infections in humans is represented by consumption of contaminated seafood. However, interestingly, as we will describe in this sub-chapter the molecular inactivation by natural antimicrobials seems to be similar to *Campylobacter* spp (Pinkerton et al., 2019).

Many attempts have been made to prevent disease in shrimp farms including ethanolic peel extracts of Kaffir lime (*Citrus hystrix*) and the common lime (*Citrus aurantifolia*) leading to their classification as vibrio agents (Singhapol & Tinrat, 2020). Other recent studies have suggested that the application of natural antimicrobials can reduce pathogen virulence *in vitro*, but not many studies have reported their efficacy in living animal models (Acosta-Smith et al., 2019; Huang et al., 2019; Khanjari et al., 2019; Liu et al., 2020; Phuong et al., 2020; Preetham et al., 2019; Singhapol & Tinrat, 2020; Zhou et al., 2019). However, a recent study has illustrated the great potential of a natural antimicrobial mixture (A3009) in reducing virulence patterns in *V. parahaemolyticus* strains. Initially, this mixture containing organic acids and citrus extract was able to significantly decrease the infectivity rate of *V. parahaemolyticus* strains on CHSE-214 fish cells. The resulted mechanism was conferred due to the alleviation of bacterial motility in different salt environments as well because of inhibition of the T6SS *hcp*1 and *hcp*2 gene expression. Subsequently, *in vivo* challenge test revealed significant protective mitigating effects of the antimicrobial mixture (A3009) and was concluded to boost survivability rates of shrimp populations exposed to *V. parahaemolyticus* infections (Pinkerton et al., 2019).

Further anti-vibrio strategies, based on natural antimicrobials, included the extracts of a mexican herbal plant Damiana de California (*Turnera diffusa*) were recently proved to exert a notable antibacterial activity against *V. parahaemolyticus* strains (Reyes-Becerril et al., 2020). It was suggested to improve immunological indices in longfin yellowtail (*Seriola rivoliana*) due to high antioxidant capacity and *in vitro* immunomodulatory results. Methanolic extracts of rambutan (*Nephelium lappaceum*) peel revealed the most increased antimicrobial potential towards *V. parahaemolyticus*, *V. campbellii*, *V. anguillarum* as well as other bacterial species (Phuong et al., 2020). The author stated that the antioxidant capacity with the enhanced antibacterial action of the extract was probably due to the availability of several phenolic compounds such as corilagin, geraniin, rutin, quercetin and ellagic acid. Similarly, anthocyanin and proanthocyanidin fraction extracted from Chinese wild blueberry (*Vaccinium uliginosum*) displayed the highest *in vitro* impact against *V. parahaemolyticus* via extravasation of nucleic acid and protein (Zhou et al., 2020). A similar mechanism was observed in Coenzyme Q0 (CoQ0) (Zheng et al., 2020). The enzyme showed to substantially attenuate the development of mature biofilms formed by *V. parahaemolyticus* on metallic surfaces as well as in fresh shrimp samples. Overall, the author concluded that Coenzyme Q0 exercises its antibacterial mechanism via the extension of microbial lag phase, afterwards triggering a negative bacterial shrinkage followed by a decrease of membrane integrity and then causing a release of bacterial content (Zheng et al., 2020).

Moreover, two potential immune molecules from the lectin class were also reported to show anti-vibrio inhibitory activity (Huang et al., 2019; Preetham et al., 2019). Firstly, a molecule (MmLec) isolated from speckled shrimp (*Metapenaeus monoceros*) haemolymph appeared to

exhibit efficiently antimicrobial properties through the alteration of biofilms formed by *Aeromonas* and *Vibrio* species (Preetham et al., 2019). Secondly, recombined collectin 11 (rCsCL-11) is molecule that was initially isolated from half-smooth tongue sole (*Cynoglossus semilaevis*) displayed a relevant antibacterial capacity against *V. anguillarum*, *V. parahaemolyticus* and other bacterial species in a eukaryotic cell line (HEK-293T). (Huang et al., 2019). According to an interesting work, fungal endophytes isolates (CAF052) from the sea anemone (*Anthopleura xanthogrammica*) showed a great inhibitory activity towards *V. harveyi* strains (Liu et al., 2020). As a suggestion, both molecules could be further examined applying to *in vivo-ex vivo* model.

7. Associations with *Clostridium* spp

The genus *Clostridium* includes approximately 200 identified species with at least 30 pathogenic species responsible for human and animal diseases. The association with *Campylobacter* spp. is rare, however it has been reported that, in a clinical study on patients suffering of infections with *Clostridium difficile,* few cases had enhanced symptoms due to co-infection with *Campylobacter* spp. (Fellmeth et al., 2010). In poultry, as in humans, *C. perfringens* is one of the etiological agents causing significant economic losses as it is responsible for the disease necrotic enteritis. These infections are usually treated with antibiotics, however, following the introduction of the European Union ban of antibiotic usage in farm production the necessity of developing novel therapeutics based on natural antimicrobials became acute (Ben Lagha et al., 2017). This effect was first demonstrated in neonatal piglets where early supplementation with Galacto-oligosaccharides has significantly reduced the presence of *Clostridium* spp., and simultaneously increased the number of *Lactobacillus* species with a direct benefit on the healthy intestinal microbiota (Tian et al., 2019). Similarly, the supplementation of poultry diets with low concentrations of nisin showed to significantly impede the proliferation of pathogenic bacteria including *C. leptum* and *C. perfringens in vivo* (Kierończyk et al., 2020). The effect seems to be based on competitive exclusion of pathogens since the application of nisin resulted in positive modulatory effects on the chicken microbiota by increasing the presence of probiotic-like bacteria. Additionally, a glycolipid (sophorolipid) synthesised from *Starmerella bombicola* presented a reasonable antimicrobial susceptibility action against *C. perfringens* (ATCC® 3624™). The author deduced that a mixture comprising lactic acid combined with sophorolipid could be applied in the role of a new natural sanitizing agent for poultry carcasses (Silveira et al., 2019).

As mentioned above the presence of probiotic like bacteria has a negative effect on *Clostridium* spp. and this has been emphasized in other studies where several species of *Bacillus* have been also recognized, *in vitro*, as having antimicrobial activity against *C. perfringens* via the production of bacteriocins. Additionally, another peptide, pediocin A synthesised by *Pediococcus pentosaceus* as well as perfrin and nisin showed to reduce significantly the growth of *C. perfringens* and *C. difficile* (Ben Lagha et al., 2017; Seal et al., 2018). An anti-clostridial peptide, Ruminococcin C, was also reported as an efficient inhibitory agent of human *C. perfringens* (Balty et al., 2019), with no toxicity against eukaryotic cells, however, exhibiting antibacterial activity in several multidrug-resistant strains (Chiumento et al., 2019).

Other natural products (as plant extracts) were also identified as having an efficient bacteriostatic and bactericidal effect against *Clostridium* spp. (Roshan et al., 2017, 2019). These products displayed antimicrobial activity within 24 h (peppermint oil, trans-cinnamaldehyde, zingerone, menthol, cinnamon root powder) against toxigenic *C. difficile* (NCTC 13366) and non-toxigenic *C. difficile* (ATCC 700057) strains. Mechanistically, these products induce a marked ATP and protein leakage in a dose-dependent manner after just 1 h of exposure. Furthermore, treatment with *Leptospermum* honey was associated with the inhibition of protein synthesis. A similar pattern was found in manuka honey described as having *in vitro* bactericidal activity and a therapeutical role in the prevention of *C. difficile* infection (Georgescu et al., 2018). The activity against *Clostridium* spp. is conferred via the non-peroxide antibacterial action of honey due to the presence of 1,2—dicarbonyl compounds and methylglyoxal. Consequently, manuka (*Leptospermum scoparium*) honey showed a potent biofilm inhibition activity *in vitro* against clinically relevant strains of *C. difficile* (Piotrowski et al., 2017). A common constituent of coconut oil, namely lauric acid, was able to significantly impair *Clostridium* spp. biofilm formation as well as promoting the formation of reactive oxygen species (Yang et al., 2018). Finally, aside from terrestrial biologically active compounds, recently marine-derived anti-clostridial novel compounds were reported (phocoenamicin and urauchimycin D) indicating inherent new sources of natural antimicrobials (Ochoa et al., 2018; Xu et al., 2018).

8. Staphylococcus spp

Alongside *Campylobacter*, *Staphylococcus* is one of the major pathogens to be controlled in the meat industry especially for its affinity to factory surfaces (Gutierrez et al., 2012). The similarities, relevant to this topic, at molecular level, refer to the 20–40% similarities between some of the efflux system proteins of *Campylobacter* and *Staphylococcus* which might be an indication of commonalities in antimicrobial resistance (Ge et al., 2005). Bacteria from the genus *Staphylococcus* includes various species as well as the common skin commensal strains and significant pathogenic strains associated with occurrences of minor, severe or fulminant infections (Gillet et al., 2019). So far, via unpredictable evolutionary processes, some *Staphylococcus* species being normal constituents of human/animal microflora have shifted towards becoming pathogen-progressive strains. For example, the observable phenomena of methicillin-resistant *S. aureus* (MRSA) was involved in the deleterious acquisition of antibacterial resistant genes, leading to fast spreadable cross-contaminations and multiple death cases (Bezerra Filho et al., 2020).

These outcomes justify the identification for novel alternatives intending to reduce *Staphylococcal* virulence characteristics, for further facilitation treatment of infections in humans or animals. Plants, bacteria, animals and fungi can be regarded as a potential source of molecules against different etiologic agents. A potent anti-*Staphylococcus aureus* activity was reported for the essential oil extracted from *Eugenia brasiliensis*, resulting in a reduction of its haemolytic activity and staphyloxanthin levels secreted by the pathogen (Bezerra Filho et al., 2020). The reduction in virulence revealed an increase in hydrogen peroxide susceptibility in *S. aureus* strains. Moreover, this oil (0.5 × MIC) affected the quorum sensing process via modulation of the *hla* and *spa* gene expression involved in the production of the alpha-haemolysin with a potential impact on the pathogen virulence (Zhang et al., 2018). Similarly, antibacterial activity was observed, *in vivo* and *in vitro*, for novel derivatives of oleanolic (OA-HDA), and maslinic acids (MA-HDA) obtained from olive oil wastes (Blanco-Cabra et al., 2019).

Many novel plant-derived antimicrobials, including their mechanism of action, are continuously discovered and described (flavane 3-ols, flavanones, flavonols, flavonoids and chalcones) against *S. aureus*, *S. epidermidis* and the methicillin-resistant strains (Farhadi et al., 2019). For example, baicalin was reported to affect cellular integrity and inhibit quorum sensing process in *S. aureus* (MRSA) strains (Zhang et al., 2020). The challenge for scientists in the case of these novel antimicrobials is to prove their activity *in vivo* since from bioflavonoids, just quercetin was approved for further clinical trials, anecdotally not for its antimicrobial potency or improved synergetic antibacterial effects with other conventional antibiotics against pathogenic bacteria. Previously defined phenolic compounds (6-prenylnaringenin and 8-prenylnaringenin) produced by *Saccharomyces cerevisiae* (GRAS strain) as well as hemiterpenoid metabolites isolated from a fungus (*Athelia rolfsii*) were also recently reported as anti-staphylococcal agents (Astuti et al., 2020; Ng et al., 2019). Besides, a separate natural fungal product (CJ-15,801) was

reported for only selective antibiotic activity towards *S. aureus* pathogenic strains (Domingo et al., 2019).

The use of natural antimicrobials to improve the efficiency of current antibiotics is a new concept of major importance especially in the case of highly resistant pathogens as it has the potential to reduce and cure bacterial infections. This concept is nicely exemplified in the case of hydroethanolic extract of *Ximenia americana* stem bark which was able to improve the antimicrobial potency of norfloxacin against *S. aureus* (ATCC 25923) displaying decreased toxicity indices in mouse fibroblasts (NCTC929) (de Menezes et al., 2019). Other studies have reported that polyphenols obtained from almond (aglycones epicatechin and catechin) displaying great inhibitory MICs indices against *S. aureus* (ATCC 6538P). Many recent studies have also suggested similar effects of other phenolics, e.g. *Callistemon citrinus* Skeels (Pulverulentone A, 8- desmethyl eucalyptin and eucalyptin), and rambutan (*Nephelium lappaceum*) peels containing geraniin, ellagic acid, corilagin and ellagic acid as significant anti-staphylococcal agents.

As mentioned during this review, beside the large variety of plant-derived bio-molecules, there is an increased interest in marine natural products. Recent findings show that staphylococcal infections were also prevented by marine compounds (desotamide, anthracimycin, nosiheptide and citreaglycon A) showing a promising *in vitro* and *in vivo* efficiency against different *Staphylococcal* including drug-resistant pathogens (Liu et al., 2019). A synthesised polypeptide (LCNKL2) from large yellow croaker (*Larimichthys crocea*) presented significant bacteriostatic and bactericidal versus *S. aureus* even when applied in low concentrations (1.5 μM) (Zhou et al., 2019). Along similar lines, the haemolymph of a centipede (*Scolopendra subspinipes*) was noted for its *in vitro* antimicrobial and low cytotoxic activity of inhibiting approximately 90% MRSA (Ali et al., 2019).

9. Conclusion

Overall, the findings of this review have depicted the broad antibacterial, anti-adhesive, anti-biofilm of various natural antimicrobials against pathogenic bacteria. We have presented recent data which strengthens our knowledge on the non-toxic effect of plant, animal or bacterial antimicrobials but with an increased efficiency against bacterial pathogens. With the advances in multidisciplinary research, this could pave the way for new insights which involve studies combining different complexes of antimicrobial compounds producing a synergistic or an additive action which may enhance antimicrobial potential against pathogens, simultaneously making them more economically profitable. To clarify this hypothesis, the fundamental point of view in this field is usually accompanied by experimental *in vitro*, *ex-vivo* and *in vivo* animal model studies for a more direct elucidation of intrinsic antimicrobial mechanisms. In conclusion, studies to date revealed plausible examples of natural antimicrobials including mixtures of plant extracts with organic acids, mixtures of bacteriocins as well metabolites extracted from the fungi or animals. The formulations mentioned above could play an indicative sustainable role in the near future due to competent pathogenesis control strategies within the agriculture, medical and farm sectors.

Author contributions

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Declaration of competing interest

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